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(71) Applicant ( <i>for all designated States except US</i> ): IMPERIAL CHEMICAL INDUSTRIES PLC [GB/GB]; Imperial Chemical House, Millbank, London SW1P 3JF (GB).  (72) Inventors; and (75) Inventors/Applicants ( <i>for US only</i> ) : GARNIER, Laurent [FR/FR]; 13, allée du Trou-Normand, F-95330 Domont (FR). BURDON, James [FR/FR]; 66 Chesterwood Road, Kings Heath, Birmingham B13 0QE (FR). POWELL, Richard, Llewellyn [GB/GB]; 9 Sadler's Wells, Bunbury, Tarporley, Cheshire CW6 9NV (GB).		Published <i>With international search report.</i>

(54) Title: PRODUCTION OF PARTIALLY FLUORINATED ETHERS

(57) Abstract

A process for the fluorination of a partially fluorinated ether having the formula R-O-CH<sub>2</sub>-R' wherein R is a fluoroalkyl group having from 1 to 6 carbon atoms and R' is hydrogen, fluorine or a fluoroalkyl group having from 1 to 6 carbon atoms, provided that where R' is a fluoroalkyl group, R is not a trifluoromethyl group or a fluoroalkyl group having a difluoromethylene group at the α-position relative to the oxygen atom, which comprises contacting the partially fluorinated ether with a transition metal fluorinating agent, especially cobalt trifluoride. 1-difluoromethoxy-1,2,2,2-tetrafluoroethane may be produced where the fluorinated ether has the formula CF<sub>3</sub>-CHR-O-CH<sub>2</sub>R where each R is independently fluorine or hydrogen.

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PRODUCTION OF PARTIALLY FLUORINATED ETHERS.

This invention relates to a process for the production of higher partially fluorinated ethers, in particular

5 1-difluoromethoxy-1,2,2,2-tetrafluoroethane, from lower partially fluorinated ethers, that is a process for the fluorination of partially fluorinated ethers.

10 1-difluoromethoxy-1,2,2,2-tetrafluoroethane, commonly known and hereafter referred to as "Desflurane" is known to have valuable anaesthetic properties but processes previously proposed for its production have suffered from various disadvantages relating to the availability and toxicity of starting materials with resulting scale-up problems for the 15 production of commercial quantities.

It has recently been proposed in European Patent Publication No. 0 482 936 to produce Desflurane by the fluorination of

20 1-difluoromethoxy-2,2,2-trifluoroethane under relatively mild conditions in the vapour phase using a transition metal fluorinating agent, in particular cobalt trifluoride.

25 However, 1-difluoromethoxy-2,2,2-trifluoroethane is itself not readily prepared and the yields of Desflurane obtained by the process are not as high as may be desired, the main by-products being over-fluorinated materials which cannot therefore be further fluorinated to desflurane.

We have now found that lower fluorinated ethers (lower fluorine content) than

30 1-difluoromethoxy-2,2,2-trifluoroethane can be fluorinated using a transition metal fluorinating agent to give substantial yields of Desflurane and by-products which may be further fluorinated to Desflurane. Furthermore, such lower fluorinated

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ethers are much more readily prepared than is  
1-difluoromethoxy-2,2,2-trifluoroethane.

According to the present invention there is  
provided a process for the fluorination of a  
5 partially fluorinated ether having the formula:



wherein R is a fluoroalkyl group having from 1 to 6  
10 carbon atoms and R<sup>1</sup> is hydrogen, fluorine or a  
fluoroalkyl group having from 1 to 6 carbon atoms,  
provided that where R<sup>1</sup> is a fluoroalkyl group, R is  
not a trifluoromethyl group or a fluoroalkyl group  
having a difluoromethylene group at the  $\alpha$ -position  
15 relative to the oxygen atom, which comprises  
contacting the fluorinated ether with a transition  
metal fluorinating agent.

Preferably the group R comprises a partially  
fluorinated alkyl group having no more than one  
20 fluorine atom attached to the carbon atom at the  
 $\alpha$ -position relative to the oxygen atom, and more  
preferably the group R comprises a  
2,2,2-trifluoroethyl or 1,2,2,2-tetrafluoroethyl  
group.

25 Preferably R<sup>1</sup> is a hydrogen or fluorine atom or  
a trifluoromethyl group, particularly a hydrogen or  
fluorine atom.

We especially prefer that the group R<sup>1</sup> is a  
fluorine or hydrogen atom and the group R is a  
30 2,2,2-trifluoroethyl or 1,2,2,2-tetrafluoroethyl  
group, since these compounds readily yield  
Desflurane.

According to a preferred embodiment of the  
invention there is provided a process for the  
35 production of

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1-difluoromethoxy-1,2,2,2-tetrafluoroethane which comprises contacting a fluorinated ether having the formula



5 where each R is independently fluorine or hydrogen, with a transition metal fluoride fluorinating agent.

The starting fluorinated ethers of the preferred embodiment of the invention are therefore (i) 1,1,1-trifluoro-2-methoxyethane,  $\text{CF}_3\text{CH}_2\text{-O-CH}_3$  (ii) 10 1,1,1-trifluoro-2-fluoromethoxyethane,  $\text{CF}_3\text{CH}_2\text{-O-CH}_2\text{F}$ , (iii) 1,1,1,2-tetrafluoro-2-methoxyethane,  $\text{CF}_3\text{CHF-O-CH}_3$  and (iv) 1,1,1,2-tetrafluoro-2-fluoromethoxyethane,  $\text{CF}_3\text{CFH-O-CH}_2\text{F}$ .

15 We have found that Desflurane is produced with greater selectivity from these starting materials than when 1-difluoromethoxy-2,2,2-trifluoroethane,  $\text{CF}_3\text{CH}_2\text{-O-CF}_2\text{H}$  is employed as the starting material.

The starting materials of the present invention 20 may be readily prepared from commercially available materials. Thus, (i) may be prepared by the reaction of trifluoroethanol with dimethyl sulphate under basic conditions or by the reaction of methyl iodide with  $\text{CF}_3\text{CH}_2\text{ONa}$  and (ii) may be prepared by the liquid phase reaction of trifluoroethanol with a mixture of hydrogen fluoride and formaldehyde as described in our published International Patent Application No. WO 25 93/12057. (iii) and (iv) may be prepared as described in GB Patent No. 1537861, and DT-OS 23 40 560 referred to therein, or by the liquid phase reaction 30 of methanol and fluoral hydrate respectively with a mixture of hydrogen fluoride and formaldehyde, as described in our published International Patent Application No. WO 93/12057.

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Cobalt trifluoride is the preferred transition metal fluoride fluorinating agent but other transition metal fluoride fluorinating agents which may be employed include, for example, the fluorides of manganese, silver and cerium or alkali metal complexes of the transition metal fluorides, for example potassium tetrafluorocobaltanate, potassium tetrafluoroargentate, and potassium hexafluoronickelate.

The temperature at which the process is effected will depend to some extent upon the fluorinating power of the particular fluorinating agent employed although usually the temperature will be in the range from about 150°C to about 450°C.

Where the fluorinating agent is cobalt trifluoride, the temperature is preferably in the range from about 180°C to about 280°C, especially from about 200°C to about 260°C.

The process is conveniently operated at about atmospheric pressure, although superatmospheric or subatmospheric pressure may be employed if desired.

The process of the invention is preferably carried out in the vapour phase. The ether is preferably vaporised over a bed of the transition metal fluorinating agent. A carrier gas may be employed, for example nitrogen.

The product ether may be readily purified, for example by fractional distillation.

The invention is illustrated but not limited by the following examples in which all % are mole %.

EXAMPLE 1.

6 kilogrammes of cobalt trifluoride were charged to an electrically heated nickel reactor vessel of

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length 96cm and diameter 16cm and was continually agitated by rotating nickel paddles.

The reactor was heated to a temperature of 250°C and 50g of 1,1,1-trifluoro-2-methoxyethane was passed over the catalyst in a stream of nitrogen with a flow rate of 5 litres per hour. The reactor off gases were collected in a Drikold-cooled copper vessel and the organics were separated from hydrogen fluoride by treatment with water at 0°C. 25g of organic product was collected. The organic product was sampled and analysed by gas chromatography. The organic product contained:

60% 2-difluoromethoxy-1,2,2,2-tetrafluoroethane,  
23% 1-difluoromethoxy-2,2,2-trifluoroethane,  
6% 1,1,1,2-tetrafluoro-2-fluoromethoxyethane and  
6% 1-difluoromethoxy-1,1,2,2,2-pentafluoroethane.

#### EXAMPLE 2.

The procedure of example 1 was repeated except that the reactor was heated to 200°C. The organic product (16g) contained  
57% 2-difluoromethoxy-1,2,2,2-tetrafluoroethane,  
27% 1-difluoromethoxy-2,2,2-trifluoroethane,  
5% 1,1,1,2-tetrafluoro-2-fluoromethoxyethane and  
3% 1-difluoromethoxy-1,1,2,2,2-pentafluoroethane.

#### EXAMPLE 3.

The procedure of example 1 was repeated except that the ether passed over the cobalt trifluoride was 100g of 1,1,2,2-tetrafluoro-1-(2,2,2-trifluoro-ethoxy)ethane. The organic product (88g) contained:

35	$\text{CF}_3\text{CHFOCF}_2\text{CF}_2\text{H}$	66%
	$\text{CF}_3\text{CH}_2\text{OCF}_2\text{CF}_2\text{H}$	14%

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$\text{CF}_3\text{CH}_2\text{OCF}_2\text{CF}_3$	9%
$\text{CF}_3\text{CF}_2\text{OCF}_2\text{CF}_2\text{H}$	10%

CLAIMS.

1. A process for the fluorination of a partially fluorinated ether having the formula:

5



wherein R is a fluoroalkyl group having from 1 to 6 carbon atoms and R<sup>1</sup> is hydrogen, fluorine or a fluoroalkyl group having from 1 to 6 carbon atoms, provided that where R<sup>1</sup> is a fluoroalkyl group, R is not a trifluoromethyl group or a fluoroalkyl group having a difluoromethylene group at the  $\alpha$ -position relative to the oxygen atom, which comprises contacting the partially fluorinated ether with a transition metal fluorinating agent.

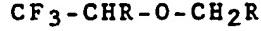
2. A process as claimed in claim 1 in which the group R comprises a 1,1,1-trifluoroethyl or 20 1,1,1,2-tetrafluoroethyl group.

3. A process as claimed in claim 1 or claim 2 in which R<sup>1</sup> is a hydrogen or fluorine atom or a trifluoromethyl group.

25

4. A process for the production of 2-difluoromethoxy-1,1,1,2-tetrafluoroethane which comprises contacting a fluorinated ether having the formula

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where each R is independently fluorine or hydrogen, with a transition metal fluoride fluorinating agent.

35

5. A process as claimed in any one of claims 1 to 4 in which the transition metal fluorinating agent is cobalt trifluoride.

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6. A process as claimed in any one of claims 1 to 5  
in which the temperature is in the range from about  
100°C to about 450°C.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 93/02035

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 C07C43/12 C07C41/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,84 02909 (THE ELECTRICITY COUNCIL) 2 August 1984 see pages 13 and 21 -----	1-3,5,6
A	EP,A,0 482 938 (RHONE-POULENC CHEMICALS) 29 April 1992 see claims; examples -----	1-6

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentstaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl.  
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Authorized officer

Wright, M

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/02035

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-8402909	02-08-84	EP-A, B	0116417	22-08-84
		GB-A, B	2133794	01-08-84
		JP-T-	60500498	11-04-85
		US-A-	4736045	05-04-88
EP-A-0482938	29-04-92	JP-A-	4273839	30-09-92